Remarks

Regarding amendments in the Claims:

Applicants have previously submitted Remarks (or Arguments) for patentability of the claims in the previously filed first Amendment/Response. Additional Remarks in this Supplemental Response are made to summarize and augment the previously submitted Remarks. The applicants believe these additional Remarks (including an illustration) will significantly aid the Examiner and significantly simplify and clarify issues involved in the prosecution of the application. As before, applicants will cite support in the specification that would be apparent to a person of ordinary skill in the art. As is well known such support need not be verbatim ("ipsis verbis" or "in haec verba"), but only described in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (see, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116). In the previously filed first Response, applicants cited well-known Written Description Requirement case law, which there is no need to cite again.

Regarding claim 7, the following support is cited. For the limitation *"wherein the CL-F region is for a species and a population and the population is a group of individuals as in the field of population genetics"*, applicants mistakenly referred the Examiner to the bottom of paragraph [0175] rather than the top of [0175] in the first Response. The top of [0175] reads ***"The CL-F region and covering markers are for a species"***; and see the next paragraph, [0176], which describes the least common allele frequency coordinate of each covering marker for the CL-F region as being based on population information. See paragraph [0135] bottom (the term population is used in a statistical sense and in the sense the term population is used in the field of population genetics; the ***"term population... is not used purely"*** or only in the sense the term is used in the field of population genetics); see also mid [0306] the term population here is used as in the field of population genetics (e.g., ***"Finnish populations... more genetically heterogeneous populations"***).

For the limitations *"wherein the CL-F region is N covered to within [x, y] by the two or more bi-allelic covering markers, wherein x is less than or equal to about D_{CL} or the equivalent thereof, wherein x is short enough that it is possible for polymorphisms within the chromosomal location distance x of each other to be in linkage disequilibrium, and y is less than or equal to about 0.2, D_{CL} is equal to the largest chromosomal length, computed by any method, for which linkage disequilibrium has been observed between any polymorphisms in any population of the species, N is an integer greater than or equal to 1"* e.g., see [0178], top [0179], top [0180], and [0080]. N-covering to within various CL-F distances, denoted for example by [x, y] is described throughout the application. Paragraph [0178] describes N-covering to within a CL-F distance, and the tops of the next two paragraphs [0179] and [0180] describe D_{CL} (***"any chromosomal length, computed by any method, for which linkage disequilibrium has been observed"***) and the limitation of y a ***"frequency distance component" [of] about 0.2"***, and [0080] and many others describes ***"wherein N is an integer greater than or equal to one".***

The clause, *"wherein x is short enough that it is possible for polymorphisms within the chromosomal location distance x of each other to be in linkage disequilibrium",* **is not a true limitation because it does not change the scope of the claim.** This is because, as stated in the claim, each point in the CL-F region is systematically covered (and N-covered). This systematic covering requires (see definition of systematically covered [0079]) that the distance between any one covering marker that systematically or N-covers any one point in the CL-F region be small enough in the chromosomal location (x) dimension for linkage disequilibrium to be present between the covering marker and a trait-causing polymorphism (or gene) that is located at the CL-F point. The definition [0079] reads in part ***"each point in the region is within a small CL-F distance of one or more of the covering markers, wherein the magnitude of the small CL-F distance is such that there is increased power ....to detect evidence for linkage between one or more covering markers and a gene [trait-causing polymorphism] that is located at a point in the CL-F region, <u>when linkage disequilibrium is present</u> between the gene [trait-causing polymorphism] and one or more of the covering markers".*** Put simply, linkage disequilibrium cannot be present if it is not possible. Similarly see also [031], [033], [0052], [0283] ***"The inventor's calculations and observations have demonstrated the increased power ... in more common, less optimal situations when .....(2) the marker and gene [trait-causing polymorphism] are <u>in some degree of linkage disequilibrium</u>."*** Thus again, **to summarize, linkage disequilibrium must be possible for there to be increased power (and systematic covering/N-covering).** (As indicated by the square brackets in the quotes above, the terms "gene" and "trait-causing polymorphism" are used interchangeably in the application, see mid [007], mid [0059].)

For the limitation in claim 7: *"wherein the choice of covering markers is not based on the assumption that a covering marker is the trait-causing polymorphism"*, **to summarize, the specification teaches that the increased power of the novel two-dimensional linkage studies is not dependent on the assumption of the optimal situation that a covering marker is the trait-causing polymorphism (e.g., disease-causing polymorphism).** In this application, theory regarding linkage studies for disease, which is a genetic trait, is extended to any genetic trait or characteristic, see e.g., [0059], [0151]. In this application, a covering marker is like any other marker used in a linkage study, except that covering markers are used in the two-dimensional linkage studies taught in the application that "cover" CL-F regions and points, see [0072]. The choice of (covering) markers in Two-Dimensional Linkage Studies taught in this application is based on the new principle (discovered by the inventor) that association-based tests for linkage are **increased in power** as the frequencies of the trait-causing allele of a bi-allelic polymorphism and the positively associated allele of a linked bi-allelic marker become similar in magnitude; see [0285] ***"The theory of operation is based on the mathematical observation that the TDT and other association-based tests for linkage are increased in power as the frequencies of the disease-causing allele of a bi-allelic gene and the positively associated allele of a linked bi-allelic marker become similar in magnitude"*** (the terms "gene" and "trait-causing polymorphism" are used interchangeably see mid [007], mid [0059]). In the analysis of Risch and Merikangas, this **increase in power** in association studies was demonstrated only when a tested marker (or marker allele) in an association study was the disease (or trait-causing) polymorphism (or polymorphism allele) itself; see mid [0027] ***"However, Risch and Merikangas' analysis was criticized by Muller-Myhsok and Abel as being based on the optimal assumption that the analyzed allele was the disease allele itself. Muller-Myhsok and Abel concluded that researchers should be aware that the power of association studies such as the TDT can be greatly diminished in more common, less optimal situations."*** (Each marker and marker allele in an association (linkage) study is "analyzed" or "tested".) See also the bottom p. 168 and top p. 169 of the inventor's paper, which is incorporated by reference into the application, *Annals of Human Genetics*, 1998, vol. 62, pp. 159-179: ***"For their [Risch and Merikangas'] analysis, the TDT was assumed to test the disease locus itself...."***

However, the inventor has shown that there is **increased power** even when the optimal situation of testing the disease (or trait-causing) polymorphism itself is not present, i.e. even when a (covering) marker in an association study is not the disease (or trait-causing) polymorphism itself; see mid [0029]. Mid [0029] states: The inventor's ***"observations and calculations published in this paper have shown that the TDT has increased power in more common, less optimal situations as well as the less common, optimal situation cited by Muller-Myhsok and Abel. As opposed to the observation of Muller-Myhsok and Abel, the inventor's calculations indicate that association tests such as the TDT have increased power in typical situations...."***. **Thus the selection of (covering) markers for a two-dimensional linkage study as taught in the application is not dependent or necessarily based on the assumption of the optimal situation that a covering marker is the (sought) trait-causing polymorphism (itself).**

For the limitation in claim 7: *"wherein the group of two or more covering markers is not an essentially one-dimensional panel of markers for a linkage study"* the following summarizes some of the support in the specification. The new linkage studies described in the application are two-dimensional; **these new linkage studies are not the old, conventional, essentially one-dimensional techniques of the past described in the application,** see, e.g. [0019], [0020], top [0035] (i.e., conventional linkage study techniques are essentially one dimensional, focus on the dimension of chromosomal location but give little attention to the dimension of allele frequency). **Hence the group of two or more covering markers (for use in this new, two-dimensional study) is not an essentially one-dimensional panel of markers.**

For the limitation in claim 7 *"wherein the essentially one-dimensional panel is a panel not based on using similarity of marker allele frequency and possible trait-causing polymorphism allele frequency to increase the power of an association-based linkage test to detect evidence for linkage"*, **to summarize (as taught in the application) the older, conventional, essentially one-dimensional perspective (e.g., bottom [0020]) for selecting (panels of) markers has no appreciation for (and is not based on) the use of similarity of allele frequency to increase power; this older perspective focuses primarily on the one dimension of chromosomal location and gives little attention to the dimension of allele frequency.** As stated above, the choice of (covering) markers in Two-Dimensional Linkage Studies taught in this application is based on the new principle (discovered by the inventor) that association-based tests for linkage are **increased in power** as the frequencies of the trait-causing allele of a bi-allelic polymorphism and the positively associated allele of a linked bi-allelic marker become similar in magnitude; see [0285] ***"The theory of operation is based on the mathematical observation that the TDT and other association-based tests for linkage are increased in power as the frequencies of the disease-causing allele of a bi-allelic gene and the positively associated allele of a linked bi-allelic marker become similar in magnitude"*** (As stated above, the terms "gene" and "trait-causing polymorphism" are used interchangeably mid [0059] and theory for disease is extended to any genetic trait or characteristic see [0059], [0151]). Each point in a CL-F region is the possible location of a gene (trait-causing polymorphism). Systematically covering a CL-F region (that is the possible location of a gene (trait-causing polymorphism)) generally makes one or more covering markers "close" to each point in the region, see [0052], [0079]. Such systematic covering and "closeness" attempts to make the allele frequencies of one or more of the covering markers similar to the allele frequencies of each possible trait-causing polymorphism located in the region; see for example bottom [0311] ***"By testing bi-allelic markers with a broad range of allele frequencies..... one is assured of testing some bi-allelic markers whose two allele frequencies are reasonably close to the allele frequencies of an unknown bi-allelic disease locus"*** [or trait-causing polymorphism]. **Therefore, the markers in two-dimensional linkage studies (taught by this application) are based on using similarity of marker allele frequency and possible trait-causing polymorphism allele frequency to increase the power of an association-based linkage test to detect evidence for linkage.**

The older, conventional, essentially one-dimensional panels of markers are, however, **not based on using similarity of marker allele frequency and possible trait-causing polymorphism allele frequency to increase the power of an association-based linkage test to detect evidence for linkage.** This is because the older, essentially one-dimensional approach had no appreciation of the importance of allele frequency for increasing power, see for example top [0308] ***"It is well known that increased disequilibrium ... increases evidence for linkage provided by association-based linkage tests..... However, what has not been recognized is that the specific allele frequencies of the marker locus can also have an enormous impact on the strength of evidence for linkage."*** As stated above, conventional linkage study techniques are essentially one dimensional, focus on the dimension of chromosomal location but give little attention to the dimension of allele frequency see, e.g. [0019], [0020], top [0035]. (For the record, the applicants note that the (increased) linkage disequilibrium in the well known principle quoted above from [0308] is essentially measured in a specific way: i.e. the increased disequilibrium is computed respectively as δ/δ_{max} for $\delta \geq 0$ or δ/δ_{min} for $\delta < 0$, wherein each of the δ values is a value of the coefficient of disequilibrium. This is the way (or essentially the way) that increased linkage disequilibrium is computed in the application in paragraphs [0291], [0292], in Table 2 on page 21, in AHG 98 in Tables1, 2, and 3 pp. 165, 167.) In addition, in the first Response a request has been made to amend the specification to include the well-known terms "panel of markers" and "marker panel" which have the same usage as the term "set of markers" in bottom paragraph [0018].

For claim 8 the following summarizes some of the support in the specification. The claim adds the limitation, *wherein the CL-F region is a segment-subrange*. Any CL-F region (any collection of one or more points [0050]) is an example of a CL-F region that is systematically covered by versions of the invention. A segment-subrange is an example of such a CL-F region, see [0090]; and see [0185] ***"Specific types of CL-F regions that are N covered are useful. For example, a rectangular CL-F region, a segment-subrange,..."***.

For support for claim 9, support for the limitations that begin with *"wherein the CL-F region is for a species and a population"* and that end with *"not based on using similarity of marker allele frequency and possible trait-causing polymorphism allele frequency to increase the power of an association-based linkage test to detect evidence for linkage"* has been cited above under claim 7. For the remaining limitations in the claim, see, e.g. [0160], [0220], [0237], i.e. any method of systematically covering a CL-F region is acceptable: ***"any method of systematically covering the CL-F region is acceptable"***. Such a method is taught in the Set/Subset Example paragraphs [0301] through [0325] inclusive of the Theory of Operation/Set/Subset Example [0281]. In this Set/Subset Example, a CL-F region is systematically covered using covering markers that are members of sets and subsets. See also the **Stamp Pasting Analogy** on page 16 for a brief introduction to Set/Subset covering teachings.

Each of the limitations in the claim is supported by the following quotes from the Set/subset part of the specification. The quotes are given in about the order in which the limitations appear in claim 9. See bottom paragraph [0306] ***"These chromosomal segments might or might not overlap each other, ...but the set of chromosomal segments should completely cover the entire chromosome or entire subregion of interest".*** The ***"segments are short enough that polymorphisms within each segment are likely to be in linkage disequilibrium with each other"*** (see top paragraph [0306]). See top [312] ***"within each chromosomal segment, subsets of bi-allelic markers should be identified."*** See mid [0314] ***"it is important that each subset contain more than one bi-allelic marker."*** See second sentence of [0312] reads ***"Each subset contains only bi-allelic markers having approximately the same allele frequencies."*** See [0312] mid bottom, ***"the difference between the frequencies of the less common allele of any two subset members should not exceed 0.15".*** See mid [0312], ***"However, the crucial point is that each subset should contain only bi-allelic markers belonging to one chromosomal segment."*** See top and mid top [0312] in which five subsets of markers designated A, B, C, D and E are chosen ***"within each chromosomal segment".*** See mid [0312] ***"In other versions of the invention the number of subsets is greater or less than five,..".***

The final limitation in claim 9 reads *"wherein the approximate allele frequencies of the markers in each subset are spaced approximately evenly over a subrange".* There is support for the concept (or limitation) that the approximate allele frequencies of the markers in each subset are spaced approximately evenly over the subrange 0.1 to 0.5. This support is as follows. See bottom [0311] ***"By testing bi-allelic markers with ...allele frequencies that are spaced at regular intervals between 0.5/0.5 and 0.1/0.9,..".*** And see [0312] bottom ***"also crucial ... is that the group of subsets for each chromosomal segment represent frequencies near the extremes of 0.5/0.5 and 0.1/0.9 as well as represent bi-allele frequencies between these two extremes that are approximately evenly spaced as illustrated by the group of subsets referred to above as A, B, C, D and E."*** See second sentence of [0312] reads ***"Each subset contains only bi-allelic markers having approximately the same allele frequencies."*** The following expands the support to include spacing the approximate allele frequencies of the markers in each subset approximately evenly over any subrange. See [0321] top ***"In this set/subset example, the least common allele frequency subrange 0.1 to 0.5 is used. In versions of the invention similar to the set/subset example, versions of the invention are operable and have utility for any subrange of the least common allele frequency range 0 to 0.5."*** See also mid bottom [0283] ***"the bi-allelic markers used in the study are chosen so that the least common allele frequencies of the markers vary systematically over a range or subrange".***

Each of the whereby clauses in this claim 9 merely states the result of the invention recited in the claim and is not a limitation. As stated by the Federal Circuit, "[a] 'whereby' clause that merely states the result of limitations in the claim adds nothing to the patentability and substance of the claim." Texas Instruments, Inc. v. U.S. Int'l Trade Commission, 988 F 2d 1165, 1172, 26 USPQ2d 1018, 1023 (Fed. Cir. 1993).

For support for claim 10, as above each of the whereby clauses in this claim 10 merely states the result of the invention recited in the claim and is not a limitation. The first limitation is *"wherein no two covering markers in the same subset provide nearly identical information with respect to their linkage and association with a third polymorphism".* See bottom [0316], which describes redundant markers in the same subset; ***"the two loci provide the nearly identical information with respect to their linkage and association with a third polymorphism ..... Hence one of the two bi-allelic markers would provide no additional information."*** See [0321], which states that Step 3, the elimination of pairs of redundant markers in the same subset (that provide the same information), is not essential. That elimination of redundant markers in subsets, though not essential, is done in claim 10.

The next limitation in claim 10 is *"wherein the chromosomal location coordinates of the CL-F region range over the chromosome or the subregion of interest and the least common allele frequency coordinates range over a subrange, whereby each CL-F point located on the chromosome or in the subregion of interest and within the subrange over which the least common allele frequency coordinates range is in the CL-F region, whereby the CL-F region is a rectangular region bounded by the chromosome or subregion of interest in the chromosomal location dimension and bounded by the subrange over which the least common allele frequency coordinates range in the allele frequency dimension,".* **The Set/subset Example(s) describe systematic covering of rectangular CL-F regions as described in more detail below (in the Illustration of an example Set/Subset N-covering using a CL-F map).** For this limitation, see [0050] and top [0075], a CL-F region is any collection of one or more points, which may be large or small. See also [0075] again ***"A particular CL-F region may be large or small.*** *For example the chromosomal location coordinates of CL-F points in a particular CL-F region can* ***range over an entire chromosome*** *..... Alternatively, the chromosomal location coordinates of CL-F points in a particular CL-F region can* ***range over only a small segment of chromosome****..... Similarly the least common allele frequency coordinates of CL-F points in a particular CL-F region can range over the entire least common allele frequency range 0 to 0.5. Alternatively the least common allele frequency coordinates of CL-F points in a particular CL-F region can* ***range over only a very small subrange****, for example the subrange 0.1 to 0.2 or less."*

The next limitation is *"wherein each point in the CL-F region is N-covered to within [L, y] by markers belonging to a subset, L is the length of the longest segment, y is 0.15 and N ≥ 2,"*. This limitation follows directly from the facts (stated above) that the markers in each subset belong to only one segment (whose maximum length is L), the fact that the difference between the least common allele frequencies of any two subset markers does not exceed 0.15, and that there are two or more markers in each subset.

Stamp pasting analogy The N-covering that is taught in the Set/Subset Examples(s) is analogous to a teaching to paste different sized postage stamps (of maximum length L and width 0.15, each stamp containing a subset of two or more covering markers) over a large rectangle on a piece of paper so that all the points in the large rectangle are "covered" (stamp edges are, of course, parallel to the rectangle boundaries, it is possible for the stamps to overlap). Since each point in the large rectangle is "covered" (each point is underneath one or more stamps), then each point in the large rectangle is within the two-dimensional (CL-F) distance [L, 0.15] of two or more covering markers (N ≥ 2). This is explained below in more detail with a pictorial illustration in the Illustration of an example Set/Subset N-covering using a CL-F map. The clause *"whereby each point in the CL-F region has the characteristic described in (1): (1) any one CL-F point is N-covered to within [x, y] by covering markers that belong to a segment that contains the chromosomal location coordinate of the point, x is the length of the segment, y is equal to 0.15, and N ≥ 2"* merely states the result of the invention recited in the claim and is not a limitation.

Regarding support for claim 12, this claim has the limitation *"wherein the least common allele frequency coordinates of the CL-F region range over the subrange 0 to less than 0.1"*. As stated above, the following expands the support for set/subset versions to include spacing the approximate allele frequencies of the markers in each subset approximately evenly over any subrange. See [0321] top ***"In this set/subset example, the least common allele frequency subrange 0.1 to 0.5 is used. In versions of the invention similar to the set/subset example, versions of the invention are operable and have utility for any subrange of the least common allele frequency range 0 to 0.5."*** And see mid [0311] which describes covering the subrange ***"below 0.1/above 0.9"*** (i.e. the least common allele frequency subrange 0 to less than 0.1; a bi-allelic polymorphism whose least common allele frequency is below 0.1 has a most common allele frequency above 0.9, the two frequencies sum to 1), see also, e.g. bottom [0075] which says, ***"the least common allele frequency coordinates of CL-F points in a particular CL-F region can range over only a very small subrange"*** and gives an example of a subrange (the subrange 0.1 to 0.2) of small width (0.1). This width, 0.1, is the same as the width of the subrange 0 to less than 0.1.

It should be noted that it is possible for a CL-F region that is systematically covered (e.g., N-covered) to be different or larger than the region over which the covering markers are evenly distributed. For example, in the set/subset example there are five subsets of markers (designated A, B, C, D and E) whose least common allele frequencies are between 0.1 and 0.5 (see bottom [0311] ***"By testing bi-allelic markers with ...allele frequencies that are spaced at regular intervals between 0.5/0.5 and 0.1/0.9,.."***). Yet the CL-F points that are systematically covered (or N-covered) include points with least common allele frequency coordinates less than 0.1 (see mid [0311] which describes covering the subrange ***"below 0.1/above 0.9"*** (i.e. the least common allele frequency subrange 0 to less than 0.1; a bi-allelic polymorphism whose least common allele frequency is below 0.1 has a most common allele frequency above 0.9, the two frequencies sum to 1).

More commentary on Set/Subset versions is given below with a pictorial illustration in the **Illustration of an example Set/Subset N-covering using a CL-F map.** Applicants believe that this section, just below, will aid the Examiner in further understanding support for claims herein.

Regarding support for claim 13, *"$N \geq 2$"* in claim 10 (from which claim 13 depends) literally means that N is greater than or equal to 2. As stated in [0182] ***"In general, the greater N is, the greater the power of a version of the invention for linkage studies.*** **Because the greater N is, the greater the chance that linkage is detected..".** Thus the specification supports higher values of N, i.e. N>2. See also top [0315] ***"Hence, it is important that each subset contain multiple bi-allelic markers so that there is increased likelihood that at least one of the markers will be in reasonably strong disequilibrium with a closely linked bi-allelic disease locus."*** Increasing the number of covering markers in each subset, as [0315] suggests, has the effect of increasing N.

Regarding claims 16 to 24, as stated in the first Response, the limitations in these claims are very similar or essentially the same as those in claims 7 to 15. Applicants have previously cited support in the specification for these limitations and the Examiner is respectfully referred to these comments above and in the first Response.

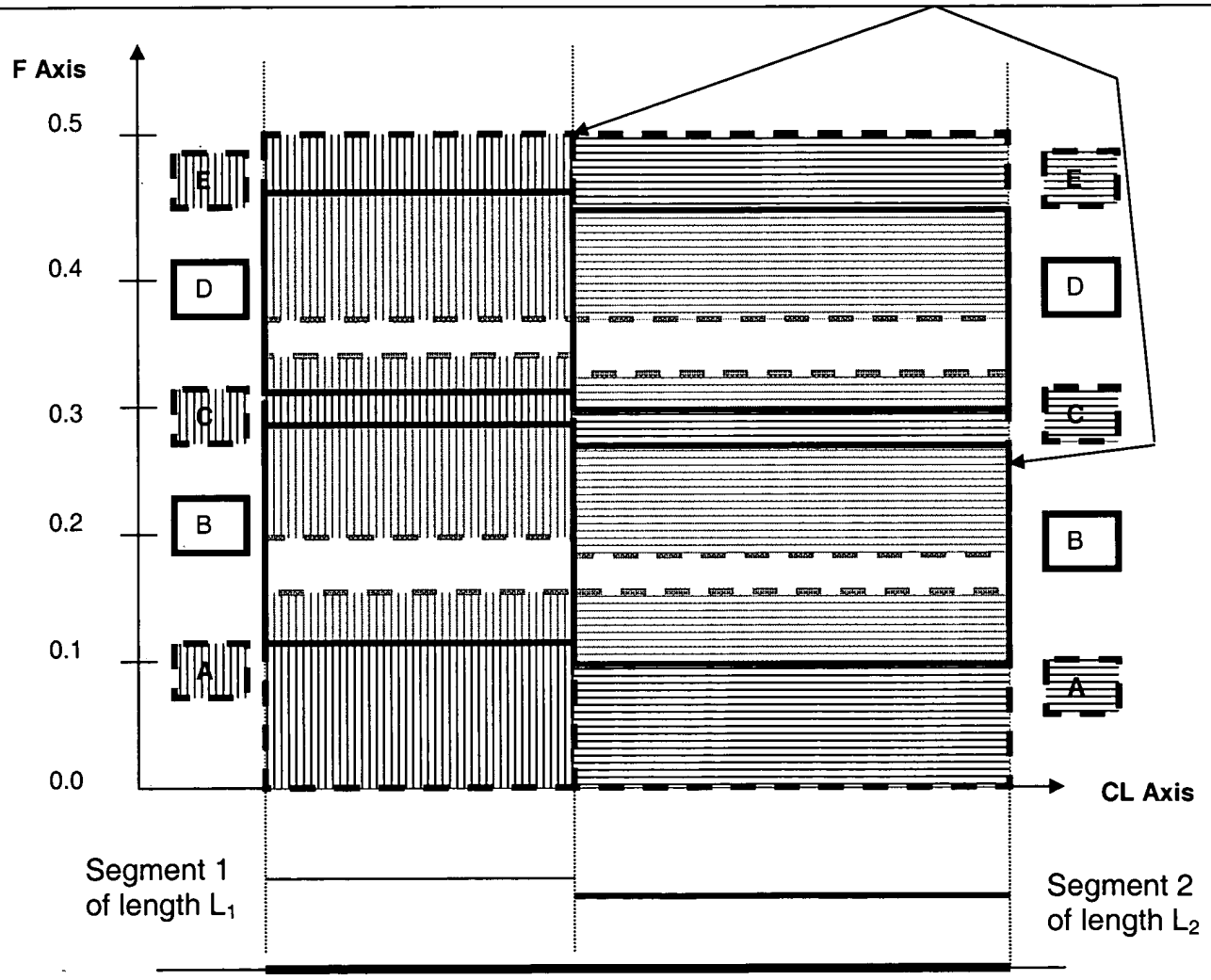
Illustration of an example Set/Subset N-covering using a CL-F map

For versions of the invention in this application, ***"Any method of systematically covering the [a] CL-F region is acceptable."*** (See paragraphs [0160], [0220], [0237]). The Set/Subset Example (paragraphs [0301] through [0325] inclusive) teaches some such methods of systematically covering a CL-F region. A nonlimiting pictorial illustration of a systematic N-covering of a large, rectangular CL-F region to within [L, 0.15], $N \geq 2$ by subsets of bi-allelic covering markers (each subset containing two or more markers) in a Set/Subset example is given below to aid the Examiner in further understanding support for claims 9, 10, 19 and 20 and claims which depend from these claims. Such an illustration is helpful, but not necessary for an understanding of versions of the invention. Such an illustration is not necessary for an understanding of any version of the invention by a person of ordinary skill in the art. Such an illustration could easily be drawn or imagined by a person of ordinary skill in the art based on the description in the application. We stress again, that this illustration (and the accompanying explanation given here), are nonlimiting.

Stamp Pasting Analogy **The systematic covering that is taught in the Set/Subset Examples is analogous to a teaching to paste different sized postage stamps (of maximum length L and width 0.15, each stamp containing a subset of two or more covering markers) over a large rectangle on a piece of paper so that all the points in the large rectangle are "covered" (stamp edges are, of course, parallel to the rectangle boundaries, it is possible for the stamps to overlap). Since each point in the large rectangle is "covered" (each point is underneath one or more stamps), then each point in the large rectangle is within the two-dimensional CL-F distance [L, 0.15] of two or more covering markers ($N \geq 2$). The pictorial illustration is given on the next page.**

Illustration of an Example Set/Subset N-covering using a CL-F map: Subsets of bi-allelic covering markers N-cover an entire, large rectangular CL-F region bounded by a chromosome or chromosomal subregion of interest in the chromosomal location (CL) dimension and bounded by the range 0 to 0.5 in the (least common allele) frequency (F) dimension.

Subsets of bi-allelic covering markers are chosen whereby each of the 10 smaller rectangular segment-subranges designated A, B, C, D or E (on the left and right) contains two or more covering markers that belong to the same subset. These 10 overlapping segment-subranges completely cover the entire, large rectangular CL-F region (arrows pointing to the top boundary and right boundary). Each of these 10 segment-subranges is less than or equal to L_2 in length and equal to 0.15 in width. So each point in the entire large rectangular region is within the two-dimensional (CL-F) distance [L_2, 0.15] of two or more covering markers. **That is, the entire large rectangular region is N-covered to within [L_2, 0.15] by the bi-allelic covering markers, wherein N ≥ 2.**



The illustration is done on a CL-F map (see paragraphs [0046], [0047], which describe CL-F maps). This CL-F map is like an x-y graph and has a chromosomal location axis (CL) and a least common allele frequency axis (F); the frequency axis (F) coordinates are given in units between 0 and 0.5 inclusive.

In this particular illustration, two nonoverlapping segments, segment 1 and segment 2, completely cover a chromosome or chromosomal subregion of interest (see bottom paragraph [0306] ***"these chromosomal segments might or might not overlap each other, ...but the set of chromosomal segments should completely cover the entire chromosome or entire subregion of interest"***.) For the sake of simplifying the illustration, two nonoverlapping segments have been chosen. Each of these segments is ***"short enough that polymorphisms within each segment are likely to be in linkage disequilibrium with each other"*** (see top paragraph [0306]).

Segment-subranges are rectangular areas on a CL-F map as described in the application (see [0090]). There are a total of ten smaller rectangular areas (segment-subranges) on this CL-F map, each of these rectangular areas corresponds to either segment 1 or to segment 2. Each such segment-subrange (or rectangular area) is labeled with a letter A, B, C, D or E, which is inside a box. The box is to the left of those segment-subranges corresponding to segment 1, and to the right of those segment-subranges corresponding to segment 2. Each lettered box has a border (solid or dashed) and an infill pattern (clear, horizontal or vertical lines) which matches to segment-subrange to which it corresponds. These segment-subranges do overlap in the frequency (vertical) dimension, and the drawing indicates this by means of semi-transparency. Because segments 1 and 2 do not overlap, the segment-subranges do not overlap in the horizontal (chromosomal location) dimension.

Each of the five segment-subranges for each chromosomal segment enclose the markers in one of 5 corresponding subsets of (covering) markers; each corresponding subset is also designated A, B, C, D and E. The approximate least common allele frequencies of the markers in each subset are approximately 0.1, 0.2, 0.3, 0.4 or 0.5 (see top [0312], ***"..subset A contains only markers whose less common allele frequency has a population frequency of about 0.1. Similarly, subsets B, C, D and E contain only bi-allelic markers whose less common allele has a frequency of approximately 0.2, 0.3, 0.4, and 0.5, respectively."***

The width of each segment-subrange is 0.15; this width follows necessarily and directly from mid bottom [0312] ***"the difference between the frequencies of the less common allele of any two subset members should not exceed 0.15".*** Similarly, the length of each segment-subrange is the length of segment 1 or the length of segment 2. This follows necessarily and directly from the fact that each subset contains only markers from one segment (see mid [0312] ***"However, the crucial point is that each subset should contain only bi-allelic markers belonging to one chromosomal segment"***). Under these circumstances, it is always possible to select one or more segment-subranges of width 0.15 and length of the segment (to which a subset markers belong) that encloses all of the markers in the subset.

Each subset contains more than one (i.e. two or more) markers (see mid [0314] ...***"it is important that each subset contain more than one bi-allelic marker"***). Thus each of the segment-subranges contains two or more markers. This follows necessarily from the description in the application given above.

Thus for any one of these segment-subranges, each CL-F point within the segment-subrange is N-covered to within [L, W], wherein L is the length of the segment, W is the width of the subrange and $N \geq 2$. This follows necessarily and directly from the fact that there are two or more markers in each subset and segment-subrange, and is apparent to a person of ordinary skill in the art. In addition, such a concept is taught in the application: (see [0099] and top [0100] ***"A CL-F matrix is a collection of segment-subranges,....Each segment-subrange in the collection (or the matrix) is a CL-F matrix cell."*** and see top [0186] ***"In the case in which there are N or more markers within each cell of a CL-F matrix, then each point within the matrix is N covered to within the CL-F distance [$L_{.CM}$, W_{CM}], wherein $L_{.CM}$ is the length of a matrix cell and W_{CM} is the width of a matrix cell."***

It is apparent and necessarily follows from the drawing that each point within the large rectangular region bounded by the chromosome or subregion of interest along the CL axis and by the range 0 to 0.5 along the frequency axis is included in at least one of the segment-subranges. (The reason that each such point is included in at least one of the segment-subranges is because of the systematic covering by the covering markers as discussed in more detail below.) This means that each point within the large rectangular region is N covered to within [L, 0.15], wherein $N \geq 2$, and L is either L_1 or L_2. Since $L_2 > L_1$, it necessarily follows that each point in the large rectangular region is N-covered to within [L_2, 0.15], wherein $N \geq 2$. That is, see the definition of N-covering to within a CL-F distance [0073], and [0070], [0071]. This definition states that ***"N is an integer number greater than or equal to 1"***; and other examples in the application are given wherein $N \geq 2$ see [0192] and [0263]. The distance [L_2, 0.15] is an example of a "covering distance" and 0.15 is an example of the "frequency distance component of the covering distance" (see [0082] and [0083]). Some examples of the frequency distance component of a covering distance being 0.15 are described in [0181] and [0223].

Such N-covering of rectangular regions (such as N-covering of rectangular segment-subranges) is described in the application. See for example [0185] ***"For example, a rectangular CL-F region, a segment-subrange, that is N-covered is used in an association based linkage study..."*** and [0178] ***"In this application, the systematic covering of a CL-F region in versions of the invention is described mathematically as the covering of a CL-F region, wherein the CL-F region is N-covered to within a CL-F distance δ.."*** and see mid [0283] ***"..the bi-allelic markers used in the study are chosen so that the least common allele frequencies of the markers vary systematically over a range or subrange of least common allele frequency AND the chromosomal location of the markers vary systematically over one or more chromosomes or chromosomal regions."*** In this application, CL-F regions are systematically covered, see [0174] and [0177]. See also [075], which states that a CL-F region may be large or small and can range over an entire chromosome or alternatively over a small segment of chromosome; and can range over the entire least common allele frequency range 0 to 0.5 or alternatively over a very small subrange such as 0.1 to 0.2 or less. It is possible for the length of the segment of a segment-subrange to be the length of an entire chromosome [0275].

As stated above, the reason that each such point in the large rectangular CL-F region (bounded by the chromosome or subregion of interest along the CL axis and by the range 0 to 0.5 along the frequency axis) is included in at least one of the segment-subranges is because this large CL-F region is systematically covered by the covering markers. This necessarily follows from [0306] bottom ***"...the set of chromosomal segments should completely cover the entire chromosome or entire subregion of interest"*** and [0312] bottom ***"also crucial ... is that the group of subsets for each chromosomal segment represent frequencies near the extremes of 0.5/0.5 and 0.1/0.9 as well as represent bi-allele frequencies between these two extremes that are approximately evenly spaced as illustrated by the group of subsets referred to above as A, B, C, D and E."*** See also bottom [0311] ***"By testing bi-allelic markers with ...allele frequencies that are spaced at regular intervals between 0.5/0.5 and 0.1/0.9, one is assured of testing some bi-allelic markers whose two allele frequencies are reasonably close to the allele frequencies of a .... bi-allelic disease locus"*** (as stated in paragraph [0311] the disease locus could be either an unknown or an unidentified disease locus).

Some other versions of the set/subset invention Other versions of the set/subset invention use more or less than five subsets: see mid [0312] ***"In other versions of the invention the number of subsets is greater or less than five.."***

Other versions of the invention eliminate Step 3, see [0321]: ***"Step 3 is not essential for the operation or utility of this version of the invention."*** Step 3 described in paragraphs [0313] through [0317] inclusive, deals with redundant markers that provide essentially no new information. Step 3 requires that no two subset markers ***"provide the same nearly identical information with respect to their linkage and association with a third polymorphism..."*** see bottom [0316].

In the version of the invention described above, the subset markers are distributed approximately evenly equally over the subrange 0.1 to 0.5. In other versions of the invention the markers are distributed approximately evenly over any other subrange: see [0321] top ***"In this set/subset example, the least common allele frequency subrange 0.1 to 0.5 is used. In versions of the invention similar to the set/subset example, versions of the invention are operable and have utility for any subrange of the least common allele frequency range 0 to 0.5."***

Conclusion

Claims 6 – 24 were previously added in the first Amendment/Response mailed December 23, 2004. Claims 7, 10, 12, 17, 20 and 22 have been slightly amended in this Supplemental Response. Amendments to claims 7, 12, 17 and 22 do not change the scope of the claims, amendments to claims 10 and 20 increases the scope of the claims. Remarks/Arguments in this Supplemental Response have been added to the Remarks/Arguments in the previously filed first Amendment/Response. Applicants believe that these additional Remarks, which include a figure or pictorial illustration, will significantly simplify and clarify issues in the prosecution of the application and will significantly aid the Examiner. (These citations of support in the Specification made in the first and second Amendment/Responses are not necessarily exhaustive for the pending claims.)

If necessary to obviate a double patenting rejection, applicants hereby file a contingent letter or notification expressly abandoning application No. 09/623, 068. **This letter or notification of express abandonment is, however, contingent upon 1) the present application no. 10/037, 718 being in good standing (not in abandonment) and 2) one or more claims in the present application no. 10/037, 718 being otherwise allowed, but requiring the abandonment of application No. 09/623,068 in order to avoid a statutory double patenting rejection.**

For the reasons advanced above, applicants respectfully submit that the application is now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,

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Mailing Certificate for Supplemental Amendment/Response dated January 26, 2005 following a first Amendment/Response to Office Action mailed December 23, 2004 for Application No. 10/037, 718. Title: Two-Dimensional Linkage Study Methods and Related Inventions, Inventors MCGINNIS and MCGINNIS

The items listed below are being deposited by me, Robert O. McGinnis, today, January 26, 2005, with First Class US mail with sufficient postage attached for delivery. The items are in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Va. 22313-1450.

The enclosed items are:

1) Supplemental Amendment/Response (signed): 24 pages including 1 figure
2) This mailing certificate (signed): 1 page.
5) One return receipt postcard.

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